INVENTION DISCLOSURE FORM

Please send the completed, signed form and all attachments to:
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Title of the Invention: **Bioluminescent CT Method and Apparatus**

I. INVENTION DESCRIPTION

1. Abstract of the Invention (250 words or less).

(a) What is the invention and what does it do?
We plan to develop a bioluminescent CT (BLCT) system to permit the detection of light emitting source distribution in 3D using multiple cameras arranged on a spherical surface. This system will facilitate rapid data collection and improves the signal-to-noise ratio. The system can also be integrated with a CT/Micro-CT scanner, as shown in Fig. 1. We will use information, associated with x-ray CT images from the same animal as the Bioluminescence scan to estimate light scatter and thus to reconstruct a 3D emission image volume registered to a corresponding CT or micro-CT image volume of anatomical and pathological structures, such as the lung and various tumors. The concept is to collect emitted photons from multiple 3D directions with respect to a living animal marked by bioluminescent compounds including reporter luciferases.

(b) For which field of application will it be useful?
The invention is mainly intended for small animal imaging, especially mouse imaging. It can be used for other biomedical applications as well, where bioluminescent signals are detectable.

(c) Why would this finding be of potential commercial value?
The bioluminescent CT device will allow for intra-organ localization of gene transcription activity with resolution capable of differentiating central airways (out to approximately the 5^{th}-7^{th} generation) activity versus parenchymal activity, and for localization of parenchymal activity in terms of sub-lobar regions. By combining an X-ray CT or X-ray micro-CT and bioluminescent CT system, the computed tomograms of chemo-luminescence would be linked to the highly detailed anatomic image sets. Note that the importance of co-registration of different modality images has been recognized, such as between PET scanning and CT. Commercial systems are now entering the clinical arena. Similarly, we expect that an integrated CT/micro-CT and bioluminescent CT system will be highly synergistic in a number of major biomedical applications, if this pilot project is successful. Furthermore, the tomographic reconstruction of bioluminescence will provide important added detail regarding regional location of reporter gene activity. By knowing the location of reporter gene activity and having micro resolution images of anatomy, we will be able to follow the link between gene activation and pathologic processes.

(d) What is the deficiency in the present technology that your invention improves?
The current bioluminescent imaging technique only takes one view of the object. Therefore, 3D structures cannot be resolved. Our conceived technique can make the bioluminescent imaging a

Exhibit B

3D tomographic modality, very much like X-ray CT advanced radiography from 2D to 3D/4D imaging.

2. Complete Description of the Invention

(a) Field(s) of application(s) or anticipated application(s) for your invention?

Our bioluminescent CT system is the first of its kind, has a great potential to upgrade the bioluminescent imaging from a 2D to 3D modality and realize the synergy by combining BLCT and micro-CT, and may revolutionize some of important biomedical research areas, especially small animal imaging at molecular levels. *This invention will greatly enhance any activity seeking to target genetic activity in a particular organ system.*

(b) Specific problem that your invention overcomes.

By integrating the x-ray and optical imaging together, we will achieve optical tomography resolution not possible with a stand-alone optical system. From a corresponding micro-CT image volume, we will gain *prior* knowledge of the underlying distribution of the optical scatters. This leverage is critical for us to stabilize this otherwise highly ill-posed optical CT problem. Specifically, we are able to directly solve for the emitting source distribution, avoiding the need for reconstruction of the optical properties in 3D. Technically, due to the integration of the micro and bioluminescent CT scanners, the nonlinear optical CT problem is transformed into a much more stable linear problem. Therefore, we will be able to significantly improve image reconstruction with the bioluminescent CT scanner.

(c) Describe the invention and its uses. Please focus on the novel aspect of the invention.

Our proposed BLCT significantly differs from the popular diffuse CT. Diffuse CT computes distributions of absorption and scattering coefficients from scattered light transmitted through an object. Typically, intensity-modulated light sources are used. Forward calculations can be performed based on a multi-grid finite-difference solution of the frequency domain diffusion equation. It is well known that diffuse CT without prior knowledge would produce poor image resolution; particularly as the background heterogeneity increases. On the other hand, BLCT assumes that the optical properties of the object are *already* known, and then it computes the photon-emitting source distribution. Therefore, the imaging model for BLCT is approximately linear, while that for diffuse CT is nonlinear. Because diffuse CT has been established as a useful modality, we are confident that BLCT should surely produce critical information, since linear inverse problems are generally easier to solve than nonlinear ones.

Even with attenuation and scattering taken into account based on a micro-CT image volume, a discrete BLCT imaging model can still be linearly expressed as $Ax = b$, where the observed data $b = \left(b^1, \cdots, b^M\right) \in R^M$, original emitting source distribution $x = \left(x_1, \cdots, x_M\right) \in R^N$, and a known non-zero $M \times N$ matrix $A = \left(A_{ij}\right)$. The problem is to reconstruct the image x from the data b.

Generally speaking, a generic BLCT algorithm consists of the following key steps: (1) reconstruction and segmentation of a micro-CT image volume, (2) association of optical properties (absorption coefficient, scattering coefficient, scattering anisotropy, and index of refraction) of soft and hard tissues to each segmented region in the micro-CT volume based on the library of optical properties, (3) determination of the coefficients of the forward imaging matrix $A = \left(A_{ij}\right)$ based on Monte Carlo simulations, (4) reconstruction of the emitting source

distribution x by inverting the matrix A, subject to the constraints imposed by the segmented anatomical structures and their optical properties.

(d) Any disadvantages or limitations of the invention that still need to be overcome.
Given the ill-posed nature of the sampling geometry, we propose to use the iterative image reconstruction approach. This strategic decision is less risky according to the conventional wisdom that the iterative approach is superior to the non-iterative approach in the case of incomplete and/or noisy data. Also, the iterative approach accommodates *prior* knowledge and imaging physics more easily. Furthermore, over the past decade, the iterative reconstruction theory, algorithms, and computing techniques have been advanced significantly.

(e) Attach any manuscripts, articles, or other documents describing the invention.
(1) BLCT R21 proposal submitted May 31, 2002
(2) BLCT R21/33 proposal submitted July 15, 2002
(3) BLCT Internal Equipment Proposal submitted July 19, 2002
Please download them from
http://dolphin.radiology.uiowa.edu/ge/BLCT

3. Current State of Development of the Invention.
(a) Cite specific results to date demonstrating that the concept is valid.
Promising data have been obtained to show the 3D BLCT potential in bioluminescent data, see Figs. 2-3.

(b) What additional research is needed to complete development and testing of the invention?
We are working hard to obtain major funding and develop a prototype.

(c) What is the time frame and estimated budget needed, if any, to further refine the invention?
We are actively working on this project. Within one year we should have a journal publication. The additional funds, such as we applied in the above mentioned two proposals, would greatly accelerate our progress.

4. Date of the Invention.
(a) Provide the date when invention was first conceived.
The concept was formed during our team discussion in early May this year.

(b) How is this date documented?
Our R21 proposal "Feasibility Study of Bioluminescent CT" documented our idea on May 31, 2002.

(c) Are laboratory records and data available?
The data are recorded as images in our R21/33 proposal on July 15, 2002. More data are collected and saved by our team.

5. Corporate Interest/Potential Licensees.
(a) What industries may be interested in the invention?
Optical imaging or micro-CT companies will be interested in this idea, particularly after we demonstrate the feasibility in peer-reviewed papers. Researchers at UCLA developed a "micro"

PET scanner and they have been inundated with requests from other university and commercial laboratories (drug companies, etc) seeking to have a similar system duplicated. After getting 200 orders behind, they have spun off a commercial company.

(c) List any specific contacts within relevant companies.
Edward Haines, PhD, Manager, Biomed. Imaging Research, Lincolnshire, IL

(c) Please indicate whether you consult with any of these companies. No.

6. Background Literature/Patents.
a) If you have conducted a literature or patent search, please list & enclose copies of relevant publications/patents.
The BLCT system we propose is the first in the world. Therefore, there is no reference available.

II. ADDITIONAL INFORMATION REQUIRED

7. Dates of Public Disclosure.
Dr. Hoffman very briefly mentioned the design in passing at an academic conference at the University of Pennsylvania in July 2002..

8. Sponsors.
No.

SIGNATURE OF UNIVERSITY OF IOWA INVENTORS ONLY

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Witnessed by:
I certify that the above invention has been explained to me and is understood by me.

Witness Signature	July 24, 2002 Date	Printed Name in Full
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